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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|-------------|----------------------|---------------------|------------------|
| 09/892,485 | 06/28/2001 | Mitsuko Ishihara | 210577US0SRD | 3202 |
| 22850 | 7590 | 06/22/2004 | EXAMINER | |
| OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C. 1940 DUKE STREET ALEXANDRIA, VA 22314 | | | FORMAN, BETTY J | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1634 | |

DATE MAILED: 06/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 09/892,485 | ISHIHARA ET AL. | |
| | Examiner | Art Unit | |
| | BJ Forman | 1634 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 29-69 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 29-69 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 28 June 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>6/01, 8/01</u> . | 6) <input type="checkbox"/> Other: ____. |

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DETAILED ACTION

1. Prosecution on the merits of this application is reopened on claims 29-69 are considered unpatentable for the reasons indicated below:

Status of the Claims

2. The examiner for this application has changed. Please address future correspondence to BJ Forman, Art Unit: 1634.

New grounds for rejection are discussed.

Claims 29-69 are under prosecution.

Information Disclosure Statement

3. The references listed on the 1449 received June and August 2001 have been reviewed and considered as indicated on the 1449 copies of which are included with this action. References lined through have not been considered by this examiner because they are not English-Language documents.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 36-37 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 36 and 37 are each indefinite for the recitation "wherein the RNA, or optionally the cDNA corresponding to the RNA" because the recitation lacks proper antecedent basis in Claim 29 which does not recited RNA or cDNA.

Claim 47 is indefinite for the recitation "the glycosylated proteins" because the recitation lacks proper antecedent basis in Claims 46 and 29.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 29-30, 53 and 67 are rejected under 35 U.S.C. 102(b) as being anticipated by Henderson et al (U.S. Patent No. 6,051,417, issued 18 April 2000).

Regarding Claim 29, Henderson et al disclose a method for detecting an endocrine disrupting action of a test substance comprising culturing a cell sensitive to an endocrine hormone in the presence of the hormone and a test substance and detecting a gene expression pattern of said cell and comparing the expression pattern to the cell cultured in the absence of

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the test substance wherein increased or decreased expression is indicative of endocrine disruption (Column 3, lines 1-60; Example 5; and Claim 1).

Regarding Claim 30, Henderson et al disclose the comparison is between presence and absence of test substance (Claim 1).

Regarding Claim 53, Henderson et al disclose the method wherein the cell is a human cell (Column 4, lines 51-62).

Regarding Claim 67, Henderson et al disclose a method for detecting an endocrine disrupting action of a test substance comprising culturing a cell sensitive to an endocrine hormone in the presence of the hormone and a test substance and detecting a gene expression pattern of said cell and comparing the expression pattern to the cell cultured in the absence of the test substance wherein increased or decreased expression is indicative of endocrine disruption (Column 3, lines 1-60; Example 5; and Claim 1).

8. Claims 29-34, 41, 45-46, 50-54, 56-58, 65-69 are rejected under 35 U.S.C. 102(b) as being anticipated by Nilsson et al (U.S. Patent No. 5,578,445, issued 26 November 1996).

Regarding Claim 29, Nilsson et al disclose a method for detecting an endocrine disrupting action of a test substance comprising culturing a cell sensitive to an endocrine hormone in the presence of the hormone (i.e. reference substance) and a test substance and detecting a gene expression pattern of said cell and comparing the expression pattern to the cell cultured in the absence of the test substance or the cell cultured in the absence of the hormone but the presence of the test substance or the cell cultured in the absence of the hormone and test substance wherein increased or decreased expression is indicative of

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endocrine disruption (Column 1, lines 39-Column 2, line 14) Furthermore, they provide specific embodiments wherein the reference sequence is estradiol (defined as a female hormone in the instant specification, page 10, lines 20-22) and the test substance is tamoxifen (Column 5, line 26-Column 6, line 23 and Claim 1).

Regarding Claim 30 Nilsson et al disclose the method wherein the expression pattern from (1) hormone with test substance is compared to (2) hormone without test substance (Column 6, lines 1-8).

Regarding Claim 31, Nilsson et al disclose the method wherein the expression pattern from (1) hormone with test substance is compared to (3) no hormone with test substance (Column 6, lines 1-8).

Regarding Claim 32, Nilsson et al disclose the method wherein the expression pattern from (1) hormone with test substance is compared to (2) hormone without test substance (3) no hormone with test substance (Column 6, lines 1-8).

Regarding Claim 33, Nilsson et al disclose the method wherein the expression pattern from (1) hormone with test substance is compared to (4) no hormone or test substance (Column 6, lines 1-8).

Regarding Claim 34, Nilsson et al disclose the method wherein the expression patterns are measured by determining the variation is the amount of gene expression i.e. protein expression regulated by gene expression (Column 3, lines 11-17).

Regarding Claim 41, Nilsson et al disclose the method wherein gene expression patterns are measured by determining a variation in the amount of protein expressed between A, B, C or D (Column 3, lines 11-17 and Column 5, line 65-Column 6, line 8).

Regarding Claim 45, Nilsson et al disclose the method wherein disruption is determined by identifying that a different amount of protein is expressed in A compared to B, C, or D (Column 3, lines 11-54).

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Regarding Claim 46, Nilsson et al disclose the method wherein gene expression patterns are measured by determining a variation in the amount of protein expressed between A, B, C or D wherein variation is indicative of disrupting activity (Column 3, lines 11-17 and Column 5, line 65-Column 6, line 8).

Regarding Claim 50, Nilsson et al disclose the method wherein the cell is a normal cell (Column 2, line 54-Column 3, line 3).

Regarding Claim 51, Nilsson et al disclose the method wherein the cell is a cancer cell (Column 5, line 26-45).

Regarding Claim 52, Nilsson et al disclose the method wherein the cell is a nonhuman cell as taught by contrast to their preferred embodiment wherein the cell is human (Column 2, lines 54-58).

Regarding Claim 53, Nilsson et al disclose the method wherein the cell is a human cell (Column 2, lines 54-58).

Regarding Claim 54, Nilsson et al disclose the method wherein the cell is not genetically engineered i.e. human cell lines MCF7 and ZR 75-1 (Column 5, lines 26-28).

Regarding Claim 56, Nilsson et al disclose the method wherein the cell is MCF7 (Column 5, lines 26-28).

Regarding Claim 57, Nilsson et al disclose the method wherein the hormone is a female hormone i.e. estradiol (defined as a female hormone in the instant specification, page 10, lines 20-22) (Column 5, lines 45-54).

Regarding Claim 58, Nilsson et al disclose the method wherein the hormone is estradiol (Column 5, lines 45-54).

Regarding Claim 65, Nilsson et al disclose a method for detecting an endocrine disrupting action of a test substance comprising culturing a cell which is not genetically engineered and which is sensitive to an endocrine hormone in the presence of the hormone (i.e. reference substance) and a test substance and detecting a gene expression pattern of said cell

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and comparing the expression pattern to the cell cultured in the absence of the test substance or the cell cultured in the absence of the hormone but the presence of the test substance or the cell cultured in the absence of the hormone and test substance wherein increased or decreased expression is indicative of endocrine disruption (Column 1, lines 39-Column 2, line 14)

Furthermore, they provide specific embodiments wherein the reference sequence is estradiol (defined as a female hormone in the instant specification, page 10, lines 20-22) and the test substance is tamoxifen (Column 5, line 26-Column 6, line 23 and Claim 1).

Regarding Claim 66, Nilsson et al disclose a method for detecting an endocrine disrupting action of a test substance comprising culturing a cell which is not genetically engineered and which is sensitive to an endocrine hormone in the presence of the hormone (i.e. reference substance) and a test substance and detecting a gene expression pattern of said cell and comparing the expression pattern to the cell cultured in the presence of the hormone and absence of the test substance wherein increased or decreased expression is indicative of endocrine disruption (Column 1, lines 39-Column 2, line 14) Furthermore, they provide specific embodiments wherein the reference sequence is estradiol (defined as a female hormone in the instant specification, page 10, lines 20-22) and the test substance is tamoxifen (Column 5, line 26-Column 6, line 23 and Claim 1).

Regarding Claim 67, Nilsson et al disclose a method for detecting an endocrine disrupting action of a test substance comprising culturing a cell which is sensitive to an endocrine hormone in the presence of the hormone (i.e. reference substance) and a test substance and detecting a gene expression pattern of said cell and comparing the expression pattern to the cell cultured in the presence of the hormone but in the absence of the test substance wherein increased or decreased expression is indicative of endocrine disruption (Column 1, lines 39-Column 2, line 14). Furthermore, they provide specific embodiments wherein the reference sequence is estradiol (defined as a female hormone in the instant

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specification, page 10, lines 20-22) and the test substance is tamoxifen (Column 5, line 26-Column 6, line 23 and Claim 1).

Regarding Claim 68, Nilsson et al disclose the method of Claim 29 wherein expression pattern from (1) is compared to (2), (3) and (4) (Column 1, lines 39-Column 2, line 14; Column 5, line 26-Column 6, line 23 and Claim 1).

Regarding Claim 69, Nilsson et al disclose the method of Claim 29 wherein expression pattern from (1) is compared to (2) and then the comparison is compared with (3) and (4) i.e. reading from the bottom up of the table found at Column 6, lines 1-5 (Column 1, lines 39-Column 2, line 14; Column 5, line 26-Column 6, line 23 and Claim 1).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. Claims 35-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nilsson et al (U.S. Patent No. 5,578,445, issued 26 November 1996) in view of Falb (U.S. Patent No. 5,849,578, issued 15 December 1998).

Regarding Claims 35-40, Nilsson et al disclose a method for detecting an endocrine disrupting action of a test substance comprising culturing a cell sensitive to an endocrine

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hormone in the presence of the hormone (i.e. reference substance) and a test substance and detecting a gene expression pattern of said cell and comparing the expression pattern to the cell cultured in the absence of the test substance or the cell cultured in the absence of the hormone but the presence of the test substance or the cell cultured in the absence of the hormone and test substance wherein increased or decreased expression is indicative of endocrine disruption (Column 1, lines 39-Column 2, line 14) Furthermore, they provide specific embodiments wherein the reference sequence is estradiol (defined as a female hormone in the instant specification, page 10, lines 20-22) and the test substance is tamoxifen (Column 5, line 26-Column 6, line 23 and Claim 1) wherein the expression patterns are measured by determining the variation is the amount of gene expression i.e. protein expression regulated by gene expression (Column 3, lines 11-17).

Nilsson does not teach determining gene expression by recovering RNA from the cells and comparing for each cell treatment the RNA or cDNA from the RNA from the treated cells to determining endocrine disruption.

However, gene expression via RNA hybridization comparisons were well known in the art at the time the claimed invention was made as taught by Falb.

Falb teaches a similar method for determining endocrine disrupting activity of a test substance comprising culturing cells in the presence and absence of the test substance and comparing gene expression to determine disruption (Column 73, line 45-Column 74, line 35). Furthermore, they provide specific preferred methods for expression comparison (sections 6.1.2 and 8.1) the methods comprising recovering the RNAs, reverse transcribing the RNA, amplifying the transcription products and subjecting the amplified products to electrophoresis (Column 16, line 53-Column 18, line 65). Falb further teaches the RNA isolation, hybridization, subtraction, amplification and detection provides identification of genes differentially expressed in samples of interest (Column 16, lines 54-59). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify

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the gene expression analysis of Nilsson et al with the RNA isolation, hybridization, subtraction, amplification and detection taught by Falb for the expected benefit of identifying sample-specific gene expression as desired in the art as taught by Falb (Column 16, lines 54-59).

11. Claims 42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nilsson et al (U.S. Patent No. 5,578,445, issued 26 November 1996) in view of Horwitz et al (U.S. Patent No. 6,750,015, filed 21 March 2001)

Regarding Claims 42-44, Nilsson et al disclose a method for detecting an endocrine disrupting action of a test substance comprising culturing a cell sensitive to an endocrine hormone in the presence of the hormone (i.e. reference substance) and a test substance and detecting a gene expression pattern of said cell and comparing the expression pattern to the cell cultured in the absence of the test substance or the cell cultured in the absence of the hormone but the presence of the test substance or the cell cultured in the absence of the hormone and test substance wherein increased or decreased expression is indicative of endocrine disruption (Column 1, lines 39-Column 2, line 14) wherein gene expression patterns are measured by determining a variation in the amount of protein expressed between A, B, C or D (Column 3, lines 11-17 and Column 5, line 65-Column 6, line 8). Nilsson et al do not teach electrophoresis, SDS-PAGE, two-dimensional electrophoresis to measure protein expression however measuring protein expression was well known in the art at the time the claimed invention was made as taught by Horwitz et al who teach a similar method for analyzing endocrine hormone responsive gene expression wherein the gene expression is determined by measuring proteins using electrophoresis e.g. SDS-PAGE (Column 49, line 55-Column 50, line 14). It would have been obvious to one of ordinary skill in the art at the time the claimed

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invention was made to modify the protein expression measuring of Nilsson et al by utilizing well known protein measurements e.g. electrophoresis, SDS-PAGE or two-dimensional electrophoresis because one of ordinary skill would have had reasonable expectation of success using well know techniques.

12. Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nilsson et al (U.S. Patent No. 5,578,445, issued 26 November 1996) in view of Dharmesh et al (Proc. Natl. Acad. Sci, USA, 1993, 90: 11127-11131).

Regarding Claim 47, Nilsson et al disclose a method for detecting an endocrine disrupting action of a test substance comprising culturing a cell sensitive to an endocrine hormone in the presence of the hormone (i.e. reference substance) and a test substance and detecting a gene expression pattern of said cell and comparing the expression pattern to the cell cultured in the absence of the test substance or the cell cultured in the absence of the hormone but the presence of the test substance or the cell cultured in the absence of the hormone and test substance wherein increased or decreased expression is indicative of endocrine disruption (Column 1, lines 39-Column 2, line 14) wherein gene expression patterns are measured by determining a variation in the amount of protein expressed between A, B, C or D (Column 3, lines 11-17 and Column 5, line 65-Column 6, line 8) but they do not teach recovering glycosylated proteins to determine expression patterns.

However, Dharmesh et al teach a similar method for detecting endocrine disruption wherein they teach that half line of the glycoprotein lutropin and biological activity at the hormone receptor level are dramatically affected by glycosylation (Abstract). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to

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modify the protein analysis of Nilsson et al by analyzing glycosylation as taught by Dharmesh et al based on the important biological effects of glycosylation as taught by Dharmesh et al (Abstract).

13. Claims 48-49, 55 and 59-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nilsson et al (U.S. Patent No. 5,578,445, issued 26 November 1996).

Regarding Claims 48-49 and 59-64, Nilsson et al disclose a method for detecting an endocrine disrupting action of a test substance comprising culturing a cell sensitive to an endocrine hormone in the presence of the hormone (i.e. reference substance) and a test substance and detecting a gene expression pattern of said cell and comparing the expression pattern to the cell cultured in the absence of the test substance or the cell cultured in the absence of the hormone but the presence of the test substance or the cell cultured in the absence of the hormone and test substance wherein increased or decreased expression is indicative of endocrine disruption (Column 1, lines 39-Column 2, line 14). Furthermore, they provide specific embodiments wherein the reference sequence is estradiol (defined as a female hormone in the instant specification, page 10, lines 20-22) and the test substance is tamoxifen (Column 5, line 26-Column 6, line 23 and Claim 1).

Nilsson et al teach method wherein endocrine disruption of a test substance is analyzed in various cell and tissues whereby effects of the test substance in the cells or tissues is analyzed (Column 2, lines 54-66) and useful as a tool for predicting effects of test substances as drug candidates (Column 1, lines 11-30). Nilsson et al further teach the preferred embodiment evaluates any steroid hormone, thyroid hormone or glucocorticoid hormones (Column 3, lines 4-8). These teachings clearly suggest the method is applicable for any cell or

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tissue sensitive to any endocrine hormone. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the specific embodiments taught by Nilsson by analyzing any cells (e.g. nerve cells or germ cells or murine) for any endocrine hormone (e.g. androgen, testosterone, adrenal cortex hormone, cortisol, aldosterone, amino acid derivative hormone, T3, T4 or parathyroid hormone) for the expected benefit of studying the effects of candidate drugs in cells of interest for modification of clinically important endocrine hormones as suggested by Nilsson et al (Column 1, lines 11-30).

Conclusion

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (571) 272-0741. The examiner can normally be reached on 6:00 TO 3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic

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Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.



BJ Forman, Ph.D.
Primary Examiner
Art Unit: 1634
June 21, 2004